REMARKS

Applicant respectfully requests reconsideration. Claims 42-53, 59-69, 71-73 and 75-80 were previously pending in this application. No claim has been amended or canceled herein. No new matter has been added.

Interview

Applicant thanks Examiner Gussow for conducting a personal interview with Arthur Krieg, Konstantin Linnik and Helen Lockhart on October 4, 2010. In the interview Applicant discussed the rejections under 35 USC 112, as described in more detail below. In particular, Applicant discussed the state of the art at the time the patent application was filed and the post filing clinical studies, including the clinical studies on CpG oligonucleotides, wherein the CpG oligonucleotides is not administered as a vaccine adjuvant.

Rejection Under 35 U.S.C. 112

Claims 42-53, 59-69, 71-73 and 75-80 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. It is stated in the Office Action that "Applicant has not shown a correlation of a cancer specific immune response with the increase of these cytokines. Applicant's specification does of not teach treatment of any cancer in any model system by administering CpG oligonucleotides." (Page 4).

In order to meet the enablement standard Applicant, in the specification, must have taught the skilled artisan how to make and use the claimed invention without undue experimentation. At the time the application was filed, the skilled artisan must have had a reasonable expectation that the claimed invention would have worked. Applicant has met this burden. Applicant's specification teaches the skilled artisan about a new class of drugs, describes the structural properties that make this class of drugs active, demonstrates the activity of such drugs, provides a nexus between the data in the specification and the claimed method, and describes how to administer the drugs to a subject in order to treat cancer. Based on these teachings, and in view of what was known in the art as described in detail below, the skilled artisan would have had a reasonable expectation that the claimed compounds would work for treating cancer.

Applicant has previously presented evidence of such in the form of pre-filing papers, as well as the teachings in the specification on how to administer the CpG ODN, and post-filing publication evidence, showing that skilled artisan's using methods such as those described in the specification were able to treat cancer and a number of clinical trials being conducted with CpG oligonucleotides, including trials for the treatment of cancer with CpG oligonucleotides. On balance, the presented evidence supports the use of CpG oligonucleotides in the treatment of cancer for at least the following reasons.

First, the invention relates to the discovery that immunostimulatory CpG oligonucleotides produce a systemic immune response in a subject that is useful in the treatment of cancer. The pattern of immune response elicited by CpG oligonucleotides exemplified in the specification is predictive of the claimed class of molecules with respect to the treatment of cancer. In fact, it had been known prior to the invention that certain types of infections and bacterial extracts trigger immune responses that can cause regression of cancers. It was the present invention that linked the immune stimulatory effects of bacterial DNA with the presence of unmethylated CpG motifs. One further aspect of the invention is the recognition that a similar type of immune response is triggered by unmethylated CpG motifs as that which is triggered by using bacterial DNA. From this discovery of the mechanism of immune activation by bacterial DNA, it may be concluded that the use of synthetic oligonucleotides containing these CpG motifs would induce a similar pattern of immune activation, and would also be capable of causing tumor regression.

As discussed in the interview, prior to filing the instant application, clinical trials had been conducted with bacterial DNA that established the use of bacterial DNA in the treatment of cancer. For example, Tokunaga et al. (Jpn. J. Infect. Dis 52, 1-11, 1999), a review article attached, describes various clinical trials involving administration of bacterial DNA to humans that demonstrated positive effects in cancer patients. Bacterial DNA was found to be effective for various cancers including malignant lymphomas, squamous cell carcinoma, cutaneous lesions of adult T cell leukemia and intraepidermal carcinomas (See page 5, item 7). Thus, as of the filing date, the skilled artisan recognized that bacterial DNA was useful in the treatment of cancer, even though the active component was unknown. In the present application, Applicant demonstrated that synthetic unmethylated CpG oligonucleotides mimicked bacterial DNA in inducing an immune response.

Furthermore, a number of clinical trials are on-going or have been performed using CpG oligonucleotides. Although in one phase III trial sufficient responses over base line chemotherapy were not observed in quantities that would commercially justify continuance of the trial, numerous other trials have demonstrated positive and encouraging results at least in some patients. For instance, a phase II trial of a CpG oligonucleotide in patients with unresectable stage IIIb/c or stage IV melanoma demonstrated objective regression of metastases and stimulated innate immune responses associated with clinical benefit in the patients (Pashenkov et al. J Clin Oncol. 2006 Dec 20;24(36):5716-24). Intralesional therapy of malignant skin tumors with CpG oligonucleotide monotherapy was found to be safe, well-tolerated and was associated with anti-tumor activity (Hofmann et al. J. Immunother 2008; 31:520-527). A CpG oligonucleotide delivered as intravenous infusion demonstrated immunologic modulation in patients with previously treated non-Hodgkin lymphoma (Link et al. J. Immunother 2006;29:558-568). Additionally, CpG oligonucleotides have been used in combination other non-adjuvant cancer therapies for the treatment of cancer in humans. The addition of a CpG oligonucleotide to taxane plus platinum chemotherapy for first-line treatment of non-small-cell lung cancer was found to improve objective responses and survival (Manegold et al. J Clin Oncol. 2008 Aug 20;26(24):3979-86). Similarly, administration of a CpG oligonucleotide in combination with rituximab to patients with relapsed and refractory non-Hodgkin's lymphoma was found to be safe and improved objective responses (Leonard et al. Clin Cancer Res. 2007; 13(20):6168-174). In these combination therapies the CpG oligonucleotide was not used as an adjuvant since no antigens were administered. Additionally, in situ vaccination with a CpG oligonucleotide induced systemic anti-lymphoma clinical responses in patients with low-grade B-cell lymphoma (Brody et al. J Clin Oncol. 2010 Oct 1;28(28):4324-32), while coadministration of a CpG oligonucleotide with antigen promoted strong antigen-specific CD8+ T cell responses in humans (Speiser et al. J. Clin. Invest. 2005; 115:739-746). Currently, at least 4 different CpG oligonucleotides have been or are being tested in clinical trials in the therapy of cancer. In Table 2 on page 478 of Krieg (Nat. Revs. 2006 v. 5), the human clinical trials being conducted or completed as of 2006 are listed. The fact that an author suggests that the medicinal chemistry of this class of molecules needs further fine-tuning at a later date does not indicate that the claimed invention lacks enablement.

The Examiner has previously cited Forni et al. and argues that certain kinds of tumors are more difficult to treat, and that in some cases responses to immunotherapy treatment are muted and/or temporary. The reference, however, mainly focuses on the results obtained for IL-12 treatment in a mouse cancer model. Forni et al. describe that immunotherapy is particularly effective against residual disease after conventional cancer therapy and in the control of tumor recurrences (see page 2571, right column, 2nd paragraph). That administration of IL-12 was less effective in treating established cancers than preventing or slowing down cancer progression of newly developing cancers is not probative to the effectiveness of unmethylated CpG oligonucleotides. because CpG induces several different cytokines, of which IL-12 is one (see, e.g., page 53, lines 26-29 of the specification).

Furthermore, the Examiner has stated that "while there are dependent claims drawn to a combination therapy, the broadest claims are drawn to a single treatment regimen." (Office Action page 5). The Examiner has not provided a clear indication of whether she considers the dependent claims drawn to the combination (43, 44 and 72, 73) to be enabled. Applicant points out for the record that the independent claim is not directed to a single treatment regimen, but rather, is broad enough to cover monotherapy as well as combination therapy.

The Office Action suggests that Krieg (J. Clin Invest. 117, p. 1184, 2007) provides teachings demonstrating the unpredictability of the use of CpG oligonucleotides as a monotherapy for the treatment of cancer. Applicant respectfully disagrees and reiterates that the claims are not limited to monotherapy. The addition of other therapeutic agents is encompassed by the broadest claims. Further, claims 43, 44, 68, 72-73, and 79-80 all specifically recite the combination of a CpG ODN with a second therapeutic agent. Moreover, the overall teachings of Krieg (2007) support the therapeutic value of CpG oligonucleotides in the treatment of diseases such as cancer. Specifically, Krieg teaches that "In mice with relatively small tumors, up to a few millimeters in diameter, CpG monotherapy can be sufficient to induce T cell-mediated tumor regression", and "In human also, monotherapy with the TLR9 agonist CPG 7909 (now called PF-3512676 when used in oncology without a vaccine) or another B-class CpG ODN, 1018 ISS, activates NK cells and induces a Th1 cytokine response in humans with B cell lymphomas." (Page 1190, first column, last paragraph). Table 2 and Table 3 provides a list of clinical trials, including phase I and phase II monotherapy

using CpG oligonucleotides. When read in its entirety Krieg is supportive of the predictability of the claimed invention.

The case law establishes that to be enabling for the claimed invention a specification has to establish that a compound and/or method of treatment is useful, it is however not required to show data demonstrating safety, effectiveness or reliability for use in humans. In In re Krimmel (292 F.2d 948 at 954, 130 USPQ 215 (CCPA 1961)) the Court held that "[t]here is nothing in the patent statute or any other statutes called to our attention which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has stated are useful for pharmaceutical applications, are safe, effective and reliable for use with humans." The court in In re Krimmel specifically rebutted the Board's assertion that any compound which has not been carried beyond the experimental stage of animal testing "may properly be regarded as of merely speculative or at best potential utility" and "that applicant will concede that in thousands of cases, promising animals tests have failed to prove out on humans" (Id., at 950). The court held that "it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans" (Id., at 953). The teachings provided in the specification clearly demonstrate to one of ordinary skill that the cytokines that are induced by unmethylated CpG oligonucleotides are useful for the treatment of cancer. The specification provides data obtained in an animal model (mice) showing induction of cytokines and B cell stimulation in the animals upon administration of unmethylated CpG oligonucleotides.

"The fact the experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re: Certain limited-charge cell culture microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983)." (See MPEP Section 2164.01). The specification teaches, and provides animal data, that cytokines that are useful for the treatment of cancer are induced upon administration of unmethylated CpG oligonucleotides. Experiments involving optimization are not undue experimentation. The use of any drug in human patients requires further optimization. Even commercially available FDA-approved drugs are subject to further research and development.

The Examiner also cited Agrawal et al (Trends in Mol Med. 2002, 8: 114-121) as teaching that different effects are observed with different CpG ODNs, and Crooke et al. (Therapeutic application of Nucleotides, R.G. Landers Co., Austin, TX, 1995) as teaching that phosphorothioate nucleotides clearly have significant limits. CpG ODN may produce variant results, with some ODNs producing more potent immune stimulation and others preferentially activating certain subsets of immune cells. However, as described in the specification, Applicant established that CpG oligonucleotides, as a class of molecules, produce an immune response that collectively is useful in the treatment of disease. Miscellaneous statements in the references cited by the Office referring to future work, fine-tuning, optimization or additional experimentation to prove clinical efficacy do not support a finding of lack of enablement for the claimed invention. While the statements may suggest that–as with any drug being developed–further experimentation is required to further develop certain aspects of the drug, they do not support the finding that such experimentation is undue with respect to the invention as claimed. In any event, they do not outweigh the direct and most pertinent evidence of enablement presented by Applicant.

In summary, Applicant's specification provides *in vitro* and *in vivo* data for a class of compounds establishing the presence of a robust immune response, and taught that such an immune response would be useful in the treatment of cancer. The skilled artisan at the time of the invention would have recognized that this assertion was true based on the data and what was known in the art at the time of the invention, i.e., that bacterial DNA was demonstrated to be useful in the treatment of cancer. Following the invention those of skill in the art, recognizing the utility of this class of therapeutics, based on the disclosure of the instant inventors, and following the guidance provided in the specification, demonstrated as the Applicant had taught that CpG ODNs were useful for treating cancer. Further, in view of the initial teachings in the art by the instant inventors numerous investigators have pursed CpG ODN as a therapeutic platform. A summary of clinical studies is provided in Krieg 2006 Nat Rev 5, p. 471, and discussed above.

In light of the credible evidence presented by Applicant that the claimed invention was enabled at the time the application was filed, reconsideration and withdrawal of the 112 rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70021US01.

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Respectfully submitted,

By 

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